



Case Report

Spectrum of Acute Kidney Injury in Pregnancy associated Thrombotic Microangiopathy

Pradnya V Manglekar^{1,*}, G Barathi¹, Subalakshmi Balasubramanian¹, S Rajendiran¹, M Jayakumar²¹Dept. of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India²Dept. of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

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ABSTRACT

Thrombotic microangiopathy (TMA) is characterized by microvascular thrombosis due to endothelial injury or abnormal platelet aggregation. It commonly manifests as microangiopathic hemolytic anaemia, thrombocytopenia and organ injury that may include acute kidney injury (AKI). It has a diverse etiology. Pregnancy associated TMA represents a secondary form that may be caused by complement mediated Hemolytic Uremic Syndrome (HUS), Thrombotic Thrombocytopenic Purpura (TTP) and preeclampsia-eclampsia. Rarely, renal cortical necrosis – a catastrophic event, may be seen in pregnancy-related TMA. We discuss three cases of thrombotic microangiopathy related to pregnancy. TMA is associated with significant fetomaternal morbidity and mortality and hence a rapid diagnosis and prompt disease management is crucial for a favourable patient outcome.

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1. Introduction

Thrombotic microangiopathy (TMA) is a pathologic term that describes presence of thrombi in the microvasculature which is secondary to endothelial injury or abnormal platelet aggregation. Laboratory investigations reveal features of microangiopathic hemolytic anaemia (MAHA), thrombocytopenia and organ injury. Various organ systems may be involved – kidney being one of the commonly involved organs.¹ Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) are the two spectrum representing TMA. Pregnancy related atypical hemolytic uremic syndrome (aHUS), pregnancy related TTP and Preeclampsia-eclampsia/HELLP syndrome represent a spectrum of various forms of Acute kidney injury that may be seen during pregnancy and postpartum period. In spite of dissimilar pathogenic mechanisms, there is considerable overlap in the clinical and laboratory manifestations of these three entities.² TMA is a life

threatening disorder and hence a timely diagnosis and multidisciplinary treatment is pivotal in saving lives.

2. Case History

3. Case 1

27 year female, chronic hypertensive since last 6 years on medical management. Past history reveals an abortion (first pregnancy) 3 years ago. During her second pregnancy, her antenatal period was uneventful upto 35 weeks of gestation when she developed severe preeclampsia. Emergency LSCS was done. She gave birth to a preterm child. Within 6 hours of delivery patient experienced severe blood loss which was managed surgically. Subsequently, she developed anasarca, oliguria which was accompanied by worsening renal function - rising serum creatinine (5.7 mg/dl; Reference range : 0.7-1.1 mg/dl) and Blood urea nitrogen (BUN) levels (59 mg/dl; Reference range: 7.9-20.1 mg/dl). Peripheral smear showed schistocytes and thrombocytopenia. LDH levels were raised (4168 U/L). Complement levels revealed normal C3 (132.8 mg/dl;

* Corresponding author.

E-mail address: pradnyam29@gmail.com (P. V. Manglekar).

Reference range: 90-180 mg/dl) and normal C4 (21.30 mg/dl; Reference range: 10-40 mg/dl). She was initiated on dialysis. In view of poor renal recovery, ultrasound guided renal biopsy was performed. Histopathological examination showed coagulative necrosis and dystrophic calcification of glomeruli and proximal tubules. (Figure 1) Proximal tubules also showed epithelial denudation. An artery showed a large thrombus occluding the lumen, fibrinoid material and mucoid degeneration of intima and myointimal hyperplasia. Medullary tissue in the biopsy showed preserved histomorphology. A final diagnosis of Renal cortical necrosis with thrombotic microangiopathy was given.

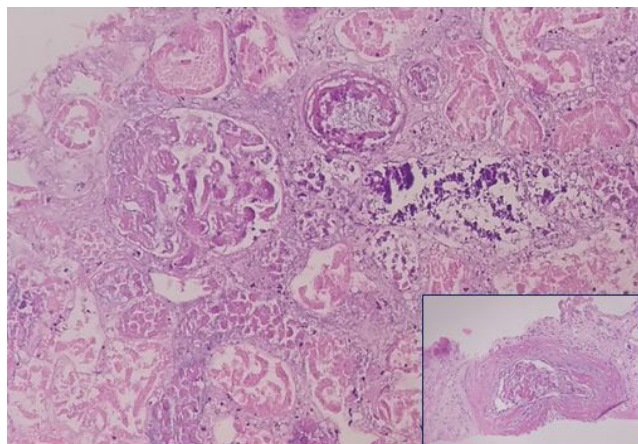


Fig. 1: H&E, 200x (Case no. 1) showing necrosis of glomeruli and tubules and foci of dystrophic calcification. Inset picture shows an artery with a large thrombus occluding the lumen, fibrinoid material and mucoid degeneration of intima and myointimal hyperplasia.

4. Case 2

25 year female, primigravida, was referred to our hospital, in view of suspected intrauterine death (IUD) at 35 weeks of gestation. History of preeclampsia was present. Emergency delivery was done after confirming IUD. Post delivery, she developed anuria, low hemoglobin (7.6 gm/dl), low platelets (88000/cumm) and raised LDH (2404 U/L). Peripheral smear showed 20% schistocytes. D-dimer levels were raised (18.33 mg/L; Reference range : Less than 0.55 mg/L FEU.). Activated partial thromboplastin time (APTT) was 32 seconds (Reference range : 20.6-30.6 seconds). Prothrombin time (PT) was normal (13.1 seconds; Reference range : 11.0-13.4 seconds). Urine routine examination showed significant proteinuria and hematuria. Antinuclear antibody test and Anti-phospholipid antibody test were negative. Serum creatinine (2.2 mg/dl) and BUN (37 mg/dl) levels were raised. Serum complement levels revealed low C3 (64.7 mg/dl) and normal C4 (15.50 mg/dl). Blood and urine cultures were negative. Hemodialysis was

initiated. Once the patient was symptomatically better with improved platelet count (above 1 lakh/cumm), renal biopsy was performed to evaluate cause of renal dysfunction. Histopathological examination showed glomeruli with segmental thickening of glomerular capillary wall due to subendothelial widening. Occasional fragmented RBC was seen in capillary lumina. Features of acute tubular injury and interstitial edema were noted. (Figure 2) Blood vessels included in the biopsy did not show any thrombi. Final diagnosis of acute tubular injury with features suspicious of Preeclampsia associated secondary TMA was given.

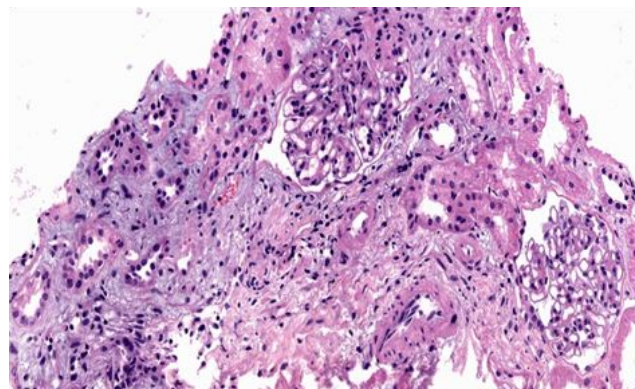


Fig. 2: H&E, 400x (Case no. 2) showing interstitial edema, subendothelial widening of glomerular capillary membrane but the blood vessels are devoid of any thrombi.

5. Case 3

30 year female, presented with complaints of facial puffiness since 1 month, pedal edema since 3 days and dyspnea on exertion since one week. She was hypertensive for past 6 months. She also had past history of right internal jugular vein thrombus and was on medication for the same. Medications were stopped since last two months. Her baseline investigations revealed raised serum creatinine (4.5 mg/dl) and raised BUN (42 mg/dl). LDH levels were raised (1382 U/L). Hemoglobin was 8.9 gm/dl. Platelet count was 1.93 lakhs/cumm (Reference range 1.50 - 4.50 lakhs/cumm). Peripheral smear showed occasional schistocyte. Serial monitoring showed worsening renal function and was initiated on hemodialysis. Her obstetric history revealed prior termination of pregnancy 6 months ago, the outcome of which was a stillbirth. She also had history of hypertension during pregnancy. In view of renal dysfunction, renal biopsy was performed. Histopathological examination showed glomeruli with double contours of glomerular basement membrane, mesangiolytic and foci of fibrinoid necrosis. (Figure 3) Features of acute tubular injury were noted. One of the blood vessel showed mucoid intimal hyperplasia and luminal narrowing (Figure 4). All these features favoured a diagnosis of TMA.

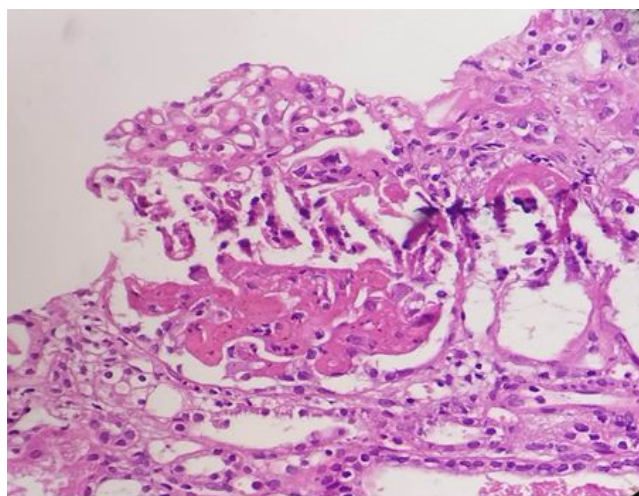


Fig. 3: H&E, 400x (Case no. 3) showing glomerulus with double contours of glomerular basement membrane, mesangiolysis and fibrinoid necrosis.

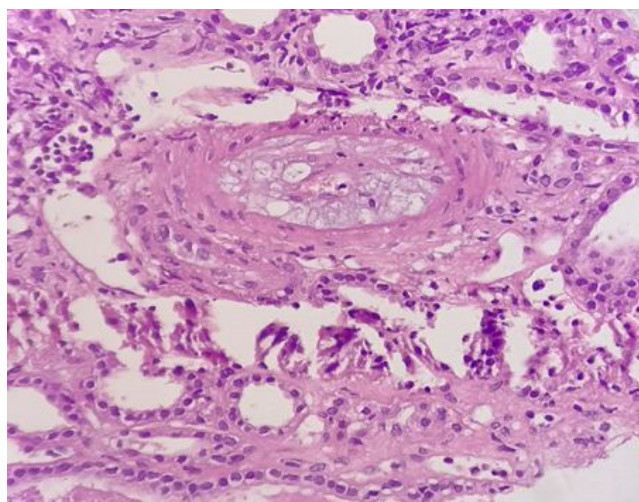


Fig. 4: H&E, 400x (Case no. 3) showing mucoid intimal hyperplasia of a blood vessel with luminal occlusion.

6. Discussion

TMA has a multifactorial etiology. Due to its diverse etiology, the classification of TMA is challenging. However, with greater understanding of pathogenic mechanisms, evolution of specific therapies and discovery of role of complement in the causation of atypical Hemolytic uremic syndrome, TMA may be broadly classified into following four categories : 1) Primary (hereditary), 2) Primary (acquired), 3) Secondary and 4) Infection associated.³ Hemolytic uremic syndrome (HUS) and TTP are commonest causes of primary TMA. These can be hereditary (mutations in genes encoding complement proteins or ADAMTS13) or acquired (autoantibody to Factor H or ADAMTS13) respectively.

We describe three interesting cases of pregnancy related thrombotic microangiopathy encountered in our institute as it is a life threatening disorder with significant fetomaternal morbidity and mortality. Two of the cases described above were associated with fetal demise (Case 2 & Case 3). Amongst these three patients, two of them (Case 1 & Case 3) succumbed to the disease inspite of optimum therapeutic interventions.

aHUS is caused by dysregulation of alternative complement pathway. This dysregulation may stem from inactivating mutations of three main inhibitory proteins - Factor H, Factor I, membrane cofactor protein (MCP). Rarely, acquired antibodies against Factor H may lead to aHUS. Similarly gain of function mutations in alternative pathway components - Factor B and C3 may lead to the formation of active C3 convertase which is resistant to the action of inhibitory factors. TTP is caused by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency which is a metalloprotease responsible for cleavage of large multimers of vonWillebrand factor. This deficiency may be constitutional or a result of acquired inhibitory antibodies against ADAMTS13. vWF multimers induce platelet aggregation that leads to formation of microthrombi in the vasculature.⁴ Preeclampsia is hypertension associated with proteinuria after 20 weeks of gestation. It may be further complicated by eclampsia (presence of Grand mal seizures) or HELLP (Hemolysis, elevated liver enzymes and low platelet count) syndrome. There is convincing evidence that pathophysiological changes occurring in preeclampsia are due to increase in circulating antiangiogenic factors - soluble Flt 1 and endoglin, which antagonize VEGF (Vascular endothelial growth factor) and TGF β (Transforming growth factor beta) signaling and thus lead to endothelial cell dysfunction, hypertension and proteinuria.⁵

Pregnancy related TTP most commonly manifests during second or third trimester. This may be attributed to progressive decrease in ADAMTS13 and simultaneous increase in vWF antigen during normal pregnancy. ADAMTS13 activity to vWF antigen ratio is lowest during second and third trimesters. This potentiates inhibitory effect of anti-ADAMTS13 autoantibodies, leading to TMA. ADAMTS13 activity less than 10% favour TTP. It is associated with severe thrombocytopenia, neurological symptoms and minor renal injury.⁴ Pregnancy associated aHUS most commonly manifests during late third trimester or postpartum. During normal pregnancy, there is complement activation in placenta. CD59 and Decay Accelerating factor – proteins produced by placenta regulate alternate complement pathway by exerting an inhibitory effect on it. Over expression of these proteins may mask the deficiency of other proteins implicated in the pathogenesis of aHUS. This protection conferred by CD59 and Decay

Accelerating Factor is lost with delivery of placenta. Other precipitating factors like postpartum hemorrhage or infection may also trigger complement activation in susceptible patients and finally culminate into HUS.⁶ HUS is associated with severe renal injury.

Amongst the above mentioned case histories, none of the patient had any past history of similar illness. It was only during present gestation / postpartum period that they presented with such a life-limiting illness. It is widely accepted that such patients harbor genetic abnormalities of the complement regulatory pathway which remain dormant for long. Pregnancy, especially when associated with complications like hypertension, postpartum hemorrhage, etc. acts as a trigger or precipitating factor rather than the primary cause of TMA that leads to such a terminal illness.

Also in one of the cases (case no.2), no vascular lesions were seen in the biopsy. As per the literature, in preeclampsia-eclampsia associated TMA, only glomerular changes in the form of subendothelial widening and acellular closure of capillary lumina are seen. Vascular changes are absent. Glomerular capillary thrombi are virtually never seen. This was in concordance with our renal biopsy findings in this patient. (Figure no.2). D-dimer levels were also elevated in this patient but PT was normal and APTT was marginally elevated. However, D-dimer is a non-specific test and apart from disseminated intravascular coagulation, it may be elevated in a number of conditions which include pregnancy and preeclampsia as well.⁷ Hence it needs to be interpreted in appropriate clinical context.

High blood pressure on admission is associated with renal insufficiency in TMA and is a strong predictor of sustained renal insufficiency.⁸ All the three patients described above had history of hypertension which probably could have acted as a contributing factor to their ailment.

Renal cortical necrosis is a rare entity usually associated with a fatal outcome. As per Sahay M. et al, obstetric causes account for 39.04% of cases of renal cortical necrosis.⁹ The obstetric causes include abruptio placenta, puerperal sepsis, post-partum HUS, postpartum hemorrhage, acute fatty liver of pregnancy, intrauterine fetal death and amniotic fluid embolism. One of our patients (case 1) showed renal cortical necrosis. With such a severe form of AKI presenting in late third trimester, pregnancy associated aHUS was strongly suspected in this case. Hence a molecular work up for entire gamut of complement mutations was done. But the molecular test report did not reveal any identifiable complement mutations. However, roughly one third of the patients may not show any identifiable complement mutation.¹⁰

In one of our patients (case no.3), although clinical features and renal biopsy findings were those of TMA, her platelet counts were normal. Similarly, in prospective phase 2 trials conducted by Legendre et al, few patients of aHUS had normal platelet counts.¹⁰ Although rare, such cases of aHUS having normal platelet counts but similar

disease outcome as seen in patients of aHUS having thrombocytopenia, have been reported in the literature.

Preeclampsia is commonly associated with complete recovery of renal function as compared to TTP and aHUS.⁴ We also observed the same in one of our patients (case no.2). Treatment of TMA should be in accordance with the underlying pathogenic mechanism for a better renal outcome. TTP is treated with plasma exchange therapy which helps replenishing the ADAMTS13 levels in blood. Some cases may be treated with B cell depleting therapy like Rituximab to suppress the production of antibodies. Eculizumab – a monoclonal antibody against C5 forms the mainstay of treatment in aHUS as it suppresses the activation of alternative complement pathway and thus prevents tissue injury. Plasma exchange therapy has a very limited utility in aHUS patients.¹⁰

To conclude, TMA is a life threatening disorder with varied manifestations. It should be suspected in cases presenting with sudden onset oligoanuria and renal dysfunction, especially in an obstetric setting. An early renal biopsy, prompt treatment and timely therapeutic intervention can prove to be a potential life saving measure in such cases.

7. Source of Funding

None.

8. Conflicts of Interest

None.

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Author biography

Pradnya V Manglekar Fellow Nephropathology

G Barathi Assistant Professor

Subalakshmi Balasubramanian Assistant Professor

S Rajendiran Professor

M Jayakumar Professor and HOD

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